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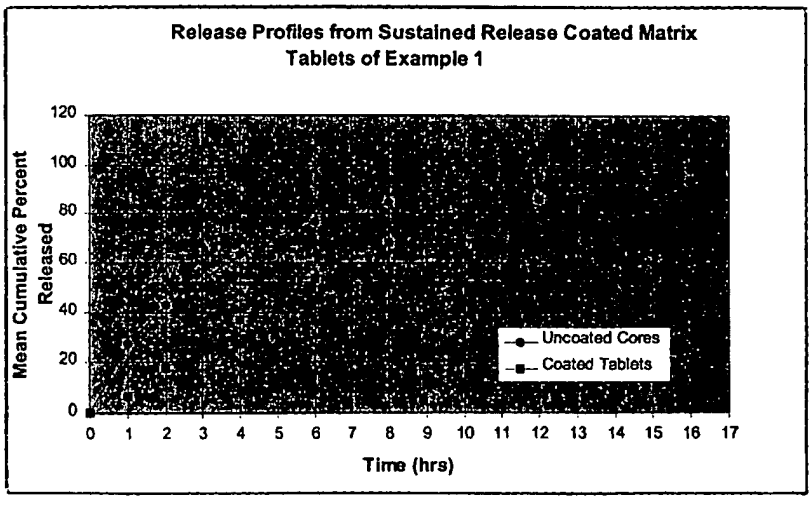

(57) Abstract: In accordance with the present invention, the release rate of a bioactive material from a hydrophilic polymer matrix core is modified by applying a water insoluble polymer membrane. The core composition as well as the membrane thickness are varied in order to achieve desired release profiles, from rapid release rate changing to near zero order release profiles with or without a lag time of up to 6 hours. The drug release from the dosage form of the invention is controlled by dual mechanism, viz., the dissolved drug first diffuses through the gelled polymer matrix and then through primarily a water insoluble polymer (semi-permeable) membrane, thereby providing the flexibility of modifying the release profiles including lag time for therapeutic agents for maximizing efficacy and patient compliance. As an illustration of this flexibility, the release profiles of Levalbuterol and Sotalol are described.

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DUAL MECHANISM TIMED RELEASE DOSAGE FORMS FOR LOW DOSE DRUGS

BACKGROUND OF THE INVENTION

In designing a controlled release oral solid dosage form, the most often sought drug release profile is a zero order or constant release rate of the active ingredient over a selected time period. Typical dosage forms capable of delivering such a release profile include an osmotic device, a tablet or a bead containing eroding matrix or a tablet or a bead coated with a water insoluble polymer membrane (reservoir-type dosage forms). US Patent 4,252,786 assigned A. L. Weiss et al. teaches the preparation of a hydrophilic matrix tablet containing a blend of 1:10 to 10:1 parts by weight polyvinylpyrrolidone and carboxyvinyl polymer and coated with a substantially water insoluble rupturable membrane. The membrane may prematurely rupture resulting in rapid release of the active ingredient from the core. US Patent 4,505,890 assigned to N.B. Jain and M.R. Patel teaches the art of making a hydrocolloidal matrix (hydroxypropyl methylcellulose, hydroxypropyl cellulose) tablet coated with a polymer blend consisting of water soluble hydroxypropyl methylcellulose and water insoluble ethylcellulose. US Patent 5,662,933 assigned to A.R. Baichwal and US Patent 5,455,046 assigned to A.R. Baichwal and T.W. McCall describe the method of making a sustained release matrix tablet formulation comprising of a blend of heteropolysaccharide and homosaccharide, and optionally a water insoluble or enteric polymer with or without a pharmaceutically acceptable excipient, the resulting tablet being coated with an enteric or water insoluble polymer. The blend of polysaccharides is preferably granulated prior to blending with the drug and other excipients. GB 2,151,921 A teaches the art of making an oral solid dosage form of Ketoprofen embedded in a hydrophilic matrix coated with a gastroresistant

coating. However, though these dosage forms sustain the release of therapeutic agents, they do not have the flexibility of providing a range of release profiles including linear release rates and especially accompanied by 3 to 6 hours lag time upon oral administration.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a method for manufacturing pharmaceutically elegant oral solid dosage forms exhibiting a range of release profiles including constant rate of release profiles for several hours. Another objective is to provide tablets with controlled lag times of up to 6 hours upon oral administration. A more particular but non-limiting further objective of the invention is to provide dosage forms (tablets or capsules containing minitablets or beads) of water soluble drugs at low doses (ranging from <1.0 (e.g., 0.5) to 30 weight %, more preferably from about 1.0 to 20 wt.% based on the total weight of the product) with desired release profiles for several hours with or without a lag time of up to about 6 hours.

Thus, one manifestation of the present invention is 1.0 mg modified release (MR) tablet formulation of Levalbuterol hydrochloride (the R enantiomer of albuterol hydrochloride) a β_2-adrenergic agonist indicated in patients for the treatment or prevention of branchospasm and asthma. The procedure for preparing Levalbuterol, an optically pure albuterol and the method of treating asthma using this isomer are well documented in the US patents assigned to Sepracor, Inc. (US Patents 5,362,755, inventors: T.J. Burberich and J.W. Young; 5,399,765, inventors: Y. Gao and C.M. Zepp; 5,545,745, inventors: Y. Gao and C.M. Zepp). These patents are incorporated in their entirety. The dosage form is prepared by compression into tablets/minitablets of a fluid bed granulation or a physical blend of pharmaceutically acceptable

excipients, one or more of hydrophilic matrix polymers, a binder and the active, the resulting tablets/minitablets being coated with primarily a water insoluble polymer. These membrane coated dosage forms exhibit a range of release profiles with or without a lag time, depending on the composition of the matrix core as well as the composition and thickness of the water insoluble membrane. The granulated wet mass may be extruded and spheronized to form core beads which are coated with primarily a water insoluble polymer. These membrane coated beads exhibit a range of release profiles with or without a lag time. A water soluble polymer may optionally be present in the water insoluble membrane formulation at from 2 to 30 wt. %, more preferably from about 5 to 20 wt. % based on the total weight of the membrane for fine tuning the release profiles of a bioactive material.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts *in-vitro* – time concentration relationships (release profiles) for certain preferred dosage forms of Example 1 in accordance with the invention.

Figure 2 demonstrates the physical stability of release profiles from tablets of Example 2 stored at accelerated conditions for up to 6 months.

Figure 3 depicts release profiles for certain dosage forms of Example 3 prepared in accordance with the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel membrane coated hydrophilic polymer matrix based oral solid dosage form having an active core provided with a minimum of one membrane barrier, namely, a membrane primarily of a water insoluble polymer applied from an aqueous or a solvent based system. The weight of the water insoluble

membrane coating varies from about 5 to 25 wt. % based on the total weight of the dosage form. The active core of the novel invention may be comprised of inert pharmaceutically acceptable excipients such as a binder, diluent, glidant, lubricant, color, flavor and the like, and one or more of hydrophilic gelling polymers. The compressible composition may be prepared by physically blending in an appropriate blender or granulated to form agglomerates by adding/spraying a granulating fluid such as water or alcohol in a fluid bed granulator such as Glatt GPCG 5 or a high shear granulator such as Fielder and compressed into conventional tablets or minitablets using a tablet press. The wet mass can be extruded and spheronized to produce drug containing spherical particles (beads) using an extruder/marumerizer. Core tablets, minitablets or beads thus prepared are coated with a water insoluble polymer membrane to further modify the release profiles. These core dosage forms may be optionally seal coated with a film forming polymer composition such as hydroxypropyl methylcellulose (Opadry Clear™ (Colorcon)), shellac or hydroxypropyl cellulose to minimize moisture related degradation and/or the interaction of the active with the components of the water insoluble membrane. Said coated tablet or beads may also have an over-coating of seal coat as a moisture barrier. The seal coat is generally applied in an amount of about 1 to 5 % of the unit weight.

Optionally, a water soluble polymer may be present in the water insoluble polymer coating formulation at about 5 to 30% w/w, thereby providing the flexibility of modifying release profiles from coated tablets, minitablets, or beads. A water soluble polymer such as HPMC or an excipient such as lactose and sodium chloride can be added to a water insoluble polymer film to increase its permeability. The composition of said water insoluble polymeric membrane as well as the individual

weights of said active cores are optimized for achieving desired release profiles for a given therapeutic agent or agents, which are predicted based on the pharmaco-kinetic and pharmaco-dynamic considerations and *in vitro/in vivo* correlation.

Dosage forms (tablets or capsules incorporating multicoated minitablets or beads) prepared in accordance with the invention may take a variety of forms. In one embodiment, the membrane coated oral solid dosage form (tablet or capsule) of the present invention may, by virtue of its significant lag time, accomplish targeted release at or near absorption sites in the gastrointestinal tract such as duodenum/jejunum or colon. In another embodiment, the capsule dosage form may employ a single form of coated minitablets or beads to provide a timed release of the drug after several hours upon oral administration. In yet another embodiment, the formulation may contain two or more minitablets or beads with different release characteristics, viz., combination of one or more modified release minitablets or beads with distinctly different lag times and release rates with or without an immediate/rapid release component to form said timed release drug delivery system. The coated minitablets or beads of two or more drugs can also be combined in a capsule dosage form to obtain synergistic efficacy and patient compliance.

Representative examples of binders suitable for granulation and bead formation include polyvinylpyrrolidone (PVP), low viscosity hydroxypropylmethyl cellulose (HPMC), low viscosity hydroxypropyl cellulose (HPC), gelatin, and corn starch. These binders are usually used in an amount of about 0.5 to 25% depending on the particular binder used. Synthetic polymers such as PVP, HPMC and HPC are typically present in an amount of about 0.5 to 10%, while gelatin and corn starch binders are typically present in an amount of about 5 to 25% depending upon the application.

Representative examples of hydrophilic gelling polymers suitable for incorporating in the formulation for producing granules by high shear or fluid bed granulation or by extrusion/spheronization include high molecular weight (e.g., about 50,000 to 100,000 molecular weight) hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylcellulose, sodium carboxymethyl cellulose, alginic acid, polymethylmethacrylate copolymers and polyvinyl acetate/crotonic acid copolymer or combinations thereof. Carboxypolymethylenes prepared from acrylic acid crosslinked with allyl ethers of sucrose or pentaerythritol are also useful as hydrophilic gelling polymers and are available commercially under the trade names CARBOPOL 934P and CARBOPOL 974P which are carbomer type polymers produced by B.F. Goodrich.

Other components of the novel formulations are optional dyes, tableting aids such as binders, fillers, glidants, and lubricants. These materials are used in conventional amounts.

Representative examples of water insoluble polymers useful in the invention include cellulose derivatives (e.g. ethylcellulose), neutral copolymers based on ethyl acrylate and methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups such as Eudragit NE, RS or RS30D, RL or RL30D and the like. The water insoluble polymers hydrate in the presence of water and swell causing the gel matrix structure to expand and break down. This break down allows drug dissolution and diffusion out of the matrix.

Representative examples of enteric polymers useful in the invention include esters of cellulose and its derivatives (cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate), polyvinyl acetate phthalate, pH-sensitive methacrylic acid-methamethacrylate

copolymers and shellac. These polymers may be used as a dry powder or an aqueous dispersion. Some commercially available materials that may be used are methacrylic acid copolymers sold under the trademark Eudragit (L100, S100, L30D) manufactured by Rohm Pharma, Cellacefate (cellulose acetate phthalate) from Eastman Chemical Co., Aquateric (cellulose acetate phthalate aqueous dispersion) from FMC Corp. and Aqoat (hydroxypropyl methylcellulose acetate succinate aqueous dispersion) from Shin Etsu K.K. The enteric polymer can be used in combination with the water insoluble polymer in an amount of about 5 to 30% by weight based on the total coating weight.

The enteric and water insoluble polymers used in forming the membranes are usually plasticized. Representative examples of plasticizers that may be used to plasticize the membranes include triacetin, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate diethyl phthalate, castor oil, dibutyl sebacate, acetylated monoglycerides and the like or mixtures thereof. The plasticizer may comprise from 3 to 30 wt. % and more typically 10 to 25 wt.% based on the polymer. The total solids in the coating system (dissolved or dispersed) depends on the polymer or polymers and the nature of the coating medium. Generally, this will be between 5 and 40 weight percent based on the total weight of the coating system.

The therapeutic agents suitable for incorporation into these Dual Mechanism Timed Release Drug Delivery Systems (DMTRDDS) include acidic, basic, zwitterion, or neutral organic/inorganic bioactive molecules or their salts. The drug substance can be selected from the group of pharmaceutically acceptable organic or inorganic chemicals with proven pharmacological activity in humans and known as analgesics, anticonvulsants, anesthetics, antidiabetic agents, anti-infective agents, antineoplastics, antiParkison agents, antirheumatic agents, cardiovascular agents, central nervous

system (CNS) stimulants, dopamine receptor agonists, gastrointestinal agents, psychotherapeutic agents, or urinary tract agents. Representative examples of therapeutic agents or drugs suitable for use in the invention include levalbuterol or its salts such as hydrochloride salt, amoxicillin, bupropion hydrochloride, carbidopa, cefaclor, diclofenac sodium, erythromycin, felodipine, loratidine, lithium carbonate, methylphenidate, metaprolol tartrate, nifedipine, omeprazole, sotalol hydrochloride, verapamil hydrochloride or a therapeutically relevant combination thereof (a combination may include drug substances not listed here). The drug content in these dosage forms varies from about 0.5 to 30.0% or more preferably from about 1.0% to 20% based on the total weight of the dosage form. Furthermore, the aqueous solubility of the drug can vary from about 0.01 to about 1,000 mg/mL.

The invention also provides a method of making a membrane coated oral solid dosage form (tablet, minitablet or bead) based on a hydrophilic gelling polymer matrix which comprises:

1. blending the active with pharmaceutically acceptable excipients including one or more of hydrophilic gelling polymers compressing into cores (tablets, minitablets and the like) or granulating using a high shear/fluid bed granulator prior to compression into cores or forming active drug containing beads by extrusion/spheronization;
2. coating said cores with a plasticized water insoluble polymer membrane which optionally may consist of a water soluble polymer at about 5 to 20% w/w;
3. coating said cores of step 1 or coated units of step 2 with Opadry or another sealant to form a coated drug delivery system (tablet, minitablet or a capsule of coated beads).

The drug substance, a binder such as PVP, a buffer, a dissolution rate controlling polymer (if used), and optionally other pharmaceutically acceptable excipients are blended together in a high shear granulator such as Fielder or a fluid bed granulator such as Glatt GPCG and granulated to form agglomerates by adding/spraying a granulating fluid such as water or alcohol and dried. The blend can also be used to produce dry granules by slugging in a tablet press or a chilsonator, without the addition of any granulating fluid. The granules thus obtained are compressed into tablets/minitablets. The wet mass can also be extruded and spheronized to produce spherical particles (beads) using an extruder/marumerizer. Said tablets/minitablets or beads may be coated with at least one membrane of water insoluble polymer in order to obtain desired release profiles.

The following Examples illustrate the manufacture of oral solid dosage forms of the invention.

Example 1

20 parts of hydroxypropyl methylcellulose (Methocel E4M Premium from Dow Chemical), 59.85 parts of microcrystalline cellulose (Avicel PH102 from FMC) and 15 parts of Carbomer (Carbopol 974P from BF Goodrich) are blended and granulated by spraying an aqueous solution of 1.15 parts of Levalbuterol hydrochloride in a fluid bed granulator, Glatt GPCG 5. 96 parts of the dried granulation is blended with 2 parts of colloidal silicon dioxide and 2 parts of magnesium stearate and compressed into 1 mg Levalbuterol tablet cores (100 mg tablet weight). The cores are coated for 6% weight gain in the fluid bed coater with an ethylcellulose dispersion (Aquacoat ECD from FMC) containing 24% dibutyl sebacate as a plasticizer based on the total weight of solids. These coated tablets are

overcoated with Opadry Clear for a weight gain of 2.0% and cured in a conventional tray drying oven at 60°C for 12 hours. The final composition of the coated 1.0 mg Levalbuterol tablet of Example 1 is as given in Table 1. Tablets are subjected to dissolution testing using USP Apparatus 2 (Paddles @ 50 rpm) in 900 mL pH 6.8 phosphate buffer. The results obtained are presented in Figure 1, which indicates a substantially constant rate of release for up to about 8 hrs or until about 70% of the dose is released.

Table 1: Formulation of Example 1

Ingredient	% w/w
Tablet Core	
Levalbuterol HCl	1.067
Avicel PH102 (Filler)	55.415
Methocel E4M	18.518
Carbopol 974P	13.889
Colloidal silicon dioxide (Glidant)	1.852
Magnesium stearate (Lubricant)	1.852
Membrane Coating	
Ethylcellulose Aqueous Dispers.	4.222
Dibutyl sebacate	1.333
Protective Coating	
Opadry Clear	1.852

Example 2

40 parts of hydroxypropyl methylcellulose (Methocel K4M Premium CR from Dow Chemical), 54.85 parts of Avicel PH102 and 1.15 parts of Levalbuterol hydrochloride are blended for 10 min in a V-blender and further blended after the addition of 2 parts of colloidal silicon dioxide and 2 parts of magnesium stearate and compressed into 1 mg Levalbuterol tablets. The cores are coated for 6% weight gain with Aquacoat dispersion. These coated tablets are coated with an Opadry protective coat and cured following the procedure of Example 1. The final compositions of the 1.0 mg Levalbuterol coated tablets of Example 2 are given in Table 2. The dissolution test results at the initial time point and for tablets stored in closed HDPE bottles at 30°C/60%RH are presented in Figure 2 indicating a stable formulation.

Table 2 : Formulation of Example 2

Ingredient	% w/w
Tablet Core	
Levalbuterol HCl	1.067
Avicel PH102	50.785
Methocel K4M	37.037
Colloidal silicon dioxide	1.852
Magnesium stearate	1.852
Membrane Coating	
Ethylcellulose Aqueous Dispers.	4.222
Dibutyl sebacate	1.333

Protective Coating	
Opadry Clear	1.852

Example 3

30 parts of Methocel K4M, 64.85 parts of Avicel PH102 and 1.15 parts of Levalbuterol hydrochloride are blended for 10 min in a V-blender and further blended after the addition of 2 parts of colloidal silicon dioxide and 2 parts of magnesium stearate and compressed into 1 mg Levalbuterol tablets. The cores are coated with Aquacoat ECD for a series of weight gains up to about 12% w/w. These coated tablets are applied an Opadry protective coating and cured following the procedure of Example 1. The final compositions of the 1.0 mg Levalbuterol coated tablets of Example 3 are as given in Table 3. The dissolution test results obtained are presented in Figure 3. The dissolution results show that lag times of one to about 6 hours can be achieved depending on the thickness of the ethylcellulose coating applied and that near linear release profiles release for several hours are observed thereafter.

Table 3 : Formulation of Example 3

Ingredient	No Coating	6.9%/2.5%	9.2%/2.3%	11.4%/2.2%
Tablet Core				
Levalbuterol HCl	1.152	1.046	1.022	0.998
Avicel PH102	64.848	58.864	57.528	56.191
Methocel K4M	30.000	27.232	26.613	25.995
Colloidal silicon dioxide	2.000	1.815	1.774	1.733
Magnesium stearate	2.000	1.815	1.774	1.733

Membrane Coating				
Ethylcellulose Disp.	0.0	5.113	6.831	8.473
Dibutyl sebacate	0.0	1.615	2.157	2.676
Protective Coating				
Opadry Clear	0.0	2.500	2.300	2.200

Example 4

30 parts of Methocel E4M, 30 parts of Avicel PH102, 16 parts of mannitol, and 20 parts of Sotalol hydrochloride are blended for 10 min in a high shear granulator and granulated with a PVP (3 parts) solution (Povidone K-30). The dried granulate is blended with one part of magnesium stearate and compressed into 20 mg minitablets. The cores are coated with Aquacoat ECD for a series of weight gains up to about 12% w/w. These coated tablets are coated with an Opadry protective coating and cured following the procedure of Example 1. The final compositions of the coated minitablets of Example 4 are given in Table 4. The dissolution results show that lag times of two to about 4 hours can be achieved depending on the thickness of the ethylcellulose coating applied and that near linear release profiles release for several hours are observed thereafter.

Table 4 : Formulation of Example 4

Ingredient	No Coating	10%/2.5%	17%/2.3%	24%/2.2%
Tablet Core				
Sotalol HCl	20.0	17.550	16.218	14.866
Avicel PH102	30.0	26.325	24.327	22.298

Methocel K4M	30.0	26.325	24.327	22.298
Mannitol (Filler)	17.0	14.917	13.785	12.636
Povidone K-30	3.0	2.632	2.433	2.230
Membrane Coating				
Ethylcellulose Disp.	0.0	7.410	12.623	17.839
Dibutyl sebacate	0.0	2.340	3.986	5.633
Protective Coating				
Opadry Clear	0.0	2.500	2.300	2.200

Example 5

20 parts of mannitol, 25 parts Methocel E4M, 10 parts of Methocel E5, 25 parts of Avicel PH102 and 20 parts of Phenytoin sodium are blended for 10 min in a V-blender and granulated with an alcohol, extruded and spheronized using NICA Extruder E-140 and Spheronizer S-450. The beads thus obtained are seal coated with a solution of shellac and membrane coated with a 50/50 blend of Eudragit RS/RL polymers for a 15% weight gain. The final composition of the 20 mg phenytoin sodium coated beads of Example 5 are given in Table 5. The dissolution results from these beads show that a lag time of about 4 hours can be achieved, followed by a near linear release for 6 hours.

Ingredient	% w/w
Tablet Core	
Phenytoin Sodium	16.49
Mannitol	16.49

Methocel K4M	30.0	26.325	24.327	22.298
Mannitol (Filler)	17.0	14.917	13.785	12.636
Povidone K-30	3.0	2.632	2.433	2.230
Membrane Coating				
Ethylcellulose Disp.	0.0	7.410	12.623	17.839
Dibutyl sebacate	0.0	2.340	3.986	5.633
Protective Coating				
Opadry Clear	0.0	2.500	2.300	2.200

Example 5

20 parts of mannitol, 25 parts Methocel E4M, 10 parts of Methocel E5, 25 parts of Avicel PH102 and 20 parts of Phenytoin sodium are blended for 10 min in a V-blender and granulated with an alcohol, extruded and spheronized using NICA Extruder E-140 and Spheronizer S-450. The beads thus obtained are seal coated with a solution of shellac and membrane coated with a 50/50 blend of Eudragit RS/RL polymers for a 15% weight gain. The final composition of the 20 mg phenytoin sodium coated beads of Example 5 are given in Table 5. The dissolution results from these beads show that a lag time of about 4 hours can be achieved, followed by a near linear release for 6 hours.

Ingredient	% w/w
Tablet Core	
Phenytoin Sodium	16.49
Mannitol	16.49

Methocel E4M	20.61
Methocel E5	8.25
Avicel PH102	20.61
Seal Coating	
Shellac	2.21
Corn Oil	0.34
Membrane Coating	
Eudragit RL polymer	12.00
Triethyl citrate	3.00

The above examples are provided to show how to practice the present invention and are not intended to be exhaustive or to include all obvious modifications and variations which will become apparent to those skilled in formulation development. However, all these modifications are within the scope of the present invention and by the following claims:

What is claimed is:

1. A pharmaceutical based dosage form comprising a core containing a drug and one or more hydrophilic gelling polymers; said core being coated with at least one water insoluble polymer membrane which is present at about 5 to 30 wt.% based on the total weight of the coated dosage form.

2. The dosage form as defined in claim 1 wherein the core particle comprises a water soluble drug, pharmaceutically acceptable excipients, and one or more hydrophilic gelling polymers.

3. The dosage form as defined in claim 2 wherein the content of the drug in the dosage form varies from 0.5 to 30% based on the total weight of the dosage form.

4. The dosage form as defined in claim 3 wherein the aqueous solubility of said drug substance varies from about 0.1 mg/mL to about 1,000 mg/mL.

5. The dosage form as defined in claim 4 wherein the drug substance is selected from the group consisting of analgesics, anticonvulsants, anesthetics, antidiabetic agents, anti-infective agents, antineoplastics, antiParkisonian agents, antirheumatic agents, cardiovascular agents, central nervous system (CNS) stimulants, dopamine receptor agonists, gastrointestinal agents, psychotherapeutic agents, and urinary tract agents.

6. The dosage form as defined in claim 5 wherein the drug substance is selected from the group consisting of levalbuterol hydrochloride, amoxicillin, bupropion

hydrochloride, carbidopa, cefaclor, diclofenac sodium, erythromycin, felodipine, loratidine, lithium carbonate, methylphenidate, metaprolol tartrate, nifedipine, omeprazole, sotalol hydrochloride, verapamil hydrochloride and therapeutically relevant combinations thereof.

7. The dosage form as defined in claim 6 wherein said core is prepared by compressing a blend of said drug, pharmaceutically acceptable excipients, hydrophilic gelling polymer(s) or by granulating and compressing, or by granulating, extruding and spheronizing.

8. The dosage form as defined in claim 7 wherein said water insoluble polymer for coating is selected from the group consisting of ethylcellulose, neutral copolymers based on ethylacrylate and methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups and combinations thereof.

9. The dosage form as defined in claim 8 wherein said membrane further comprises a plasticizer selected from the group consisting of triacetin, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate diethyl phthalate, corn oil, castor oil, dibutyl sebacate, acetylated monoglycerides and mixtures thereof.

10. The dosage form as defined in claim 9 wherein said membrane coating is applied from a solution in a pharmaceutically acceptable solvent or an aqueous dispersion of the water insoluble polymers or their mixtures.

11. The dosage form as defined in claim 10 wherein said membrane is applied to a sufficient thickness so as to achieve desired release profiles with a lag time of three to six hours upon oral administration.

12. The dosage form as defined in claim 11 further comprising a seal coat applied over the core or over the water insoluble polymer layer.

13. The dosage form as defined in claim 12 wherein said dosage form comprises a water insoluble membrane coated tablet or capsule containing water insoluble membrane coated minitablets or beads.

14. The dosage form as defined in claim 13 wherein said capsule comprises a single form of water insoluble membrane coated minitablets or beads to provide a timed-release of the drug at or near specific absorption sites at or near duodenum/jejunum or colon.

15. The dosage form as defined in claim 14 wherein said dosage form further comprises immediate or rapid release minitablets or beads containing the drug.

16. The dosage form as defined in claim 1 wherein said capsule comprises two or more forms of water insoluble membrane coated minitablets or beads with different release characteristics.

17. The dosage form as defined in claim 1 wherein said capsule comprises coated minitablets or beads of two or more drugs.

18. The dosage form of claim 1 wherein said hydrophilic gelling polymer is hydroxypropyl methylcellulose.

19. The dosage form of claim 18 wherein said water insoluble polymer membrane contains ethyl cellulose.

20. The dosage form of claim 19 wherein said drug is levalbuterol, sotalol or phenytoin sodium.

21. A method of making a pharmaceutical dosage form which comprises:

a) preparing a core tablet, minitablet or bead comprising a water soluble drug and one or more hydrophilic gelling polymers;

b) coating said drug containing core tablet, minitablet or bead with a plasticized water insoluble polymer membrane; and

c) applying a moisture barrier membrane coating on said core tablet, minitablet or bead or on said coated tablet, minitablet or bead;

wherein said water insoluble membrane provides predetermined lag time/release profiles and the weight of the water insoluble polymer membrane varies from about 5 to 25 percent based on the total weight of the coated product.

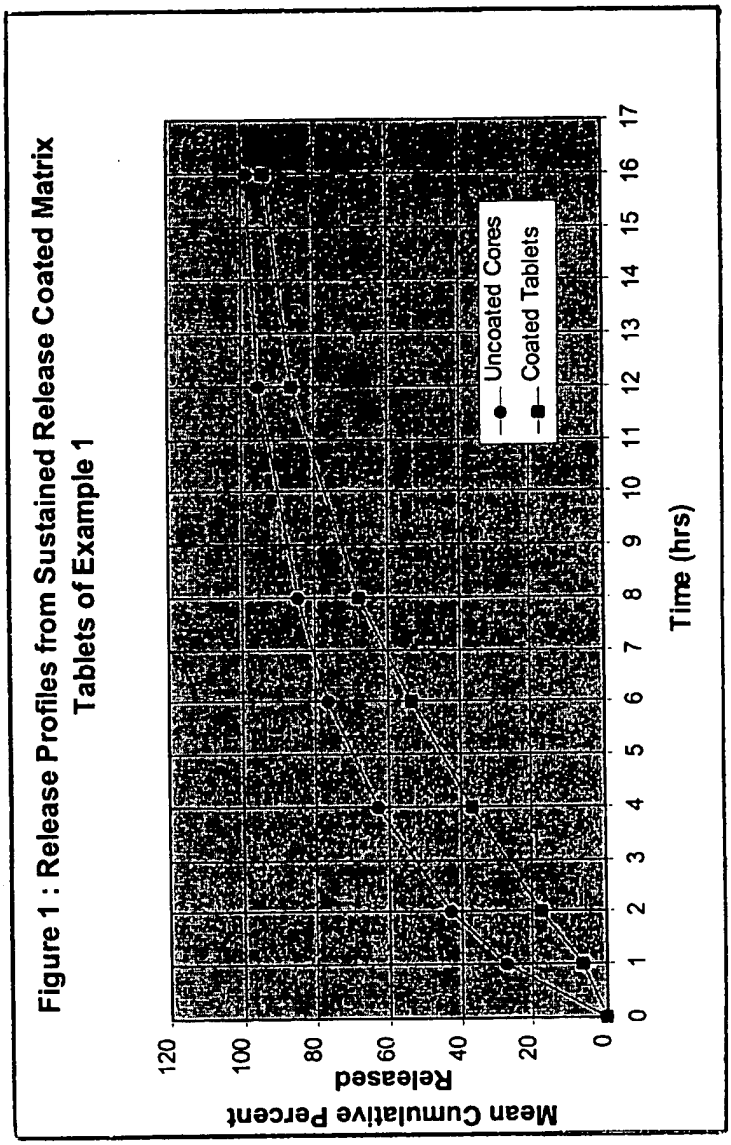
Figure 1 : Release Profiles from Sustained Release Coated Matrix Tablets of Example 1
Mean Cumulative Percent Released
120
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Time (hrs)
Uncoated Cores
Coated Tablets

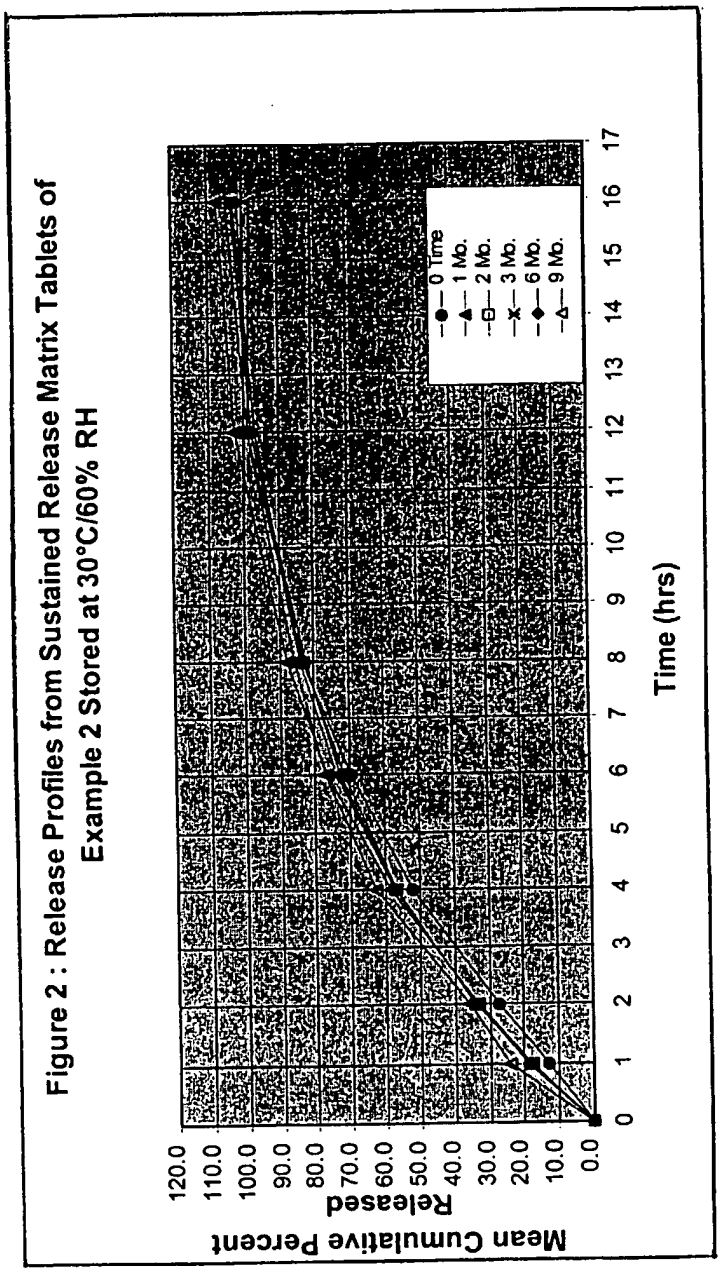
Figure 2 : Release Profiles from Sustained Release Matrix Tablets of Example 2 Stored at 30°C/60% RH
Mean Cumulative Percent Released
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Time (hrs)
0 Time
1 Mo.
2 Mo.
3 Mo.
6 Mo.
9 Mo.

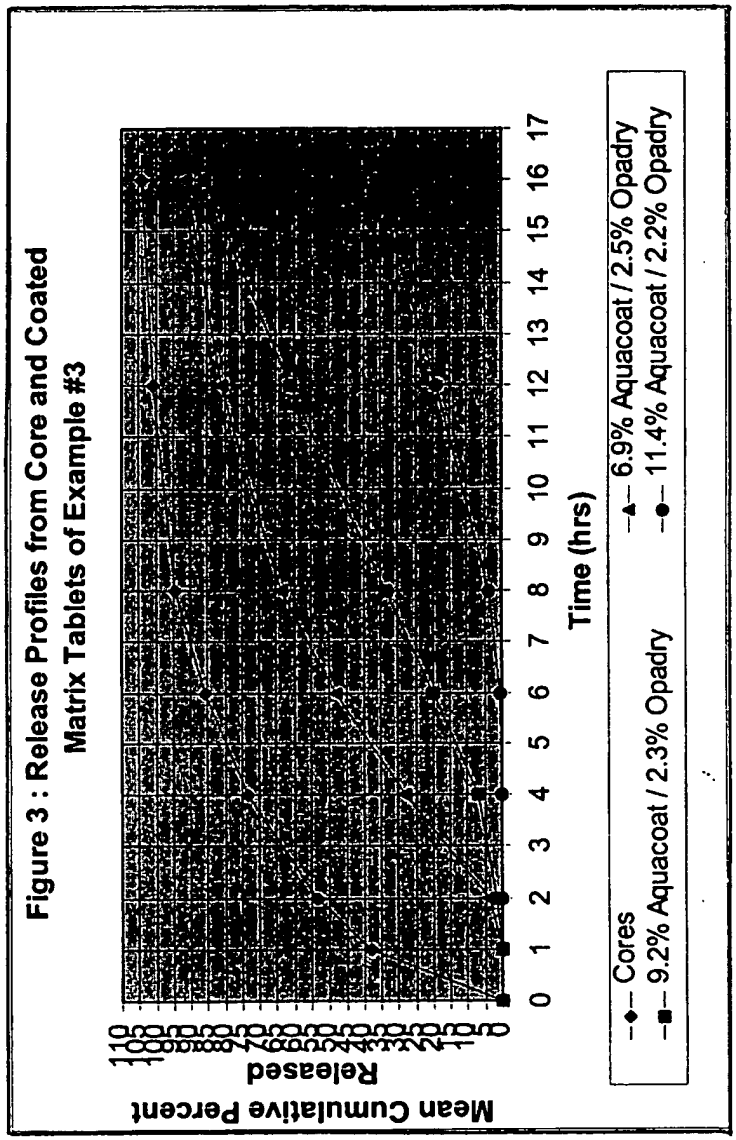
Figure 3 : Release Profiles from Core and Coated Matrix Tablets of Example #3
Mean Cumulative Percent Released
Time (hrs)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Cores
9.2% Aquacoat / 2.3% Opadry
6.9% Aquacoat / 2.5% Opadry
11.4% Aquacoat / 2.2% Opadry